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14. ABSTRACT

This cross-sectional clinical study aims to examine potential mechanisms contributing to stress fracture risk. In particular, in Study 1, we will perform advanced skeletal imaging along with gait-assessments in subjects with history of a single vs multiple vs no prior stress fractures. In addition, in Aim 2, we will perform advanced imaging to delineate variation in skeletal features according to sex and race/ethnic-origin that may contribute or protect from stress fracture. To date, we have enrolled 21 subjects in Study 1 with an additional 9 subjects scheduled for their visit. Enrollment for both Aims is ongoing. Skeletal assessments are behind schedule due to the delay in installation of the second generation high-resolution peripheral quantitative computed tomography device at MGH. As studies are ongoing, we have not performed any data analyses.

15. SUBJECT TERMS

Stress fracture, bone stress injury, gait analysis, bone microarchitecture, race/ethnic origin, sex-related differences, bone biomechanics, skeletal alignment

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Introduction

Lower extremity stress fractures are one of the most common musculoskeletal injuries plaguing military recruits, causing lost-duty days and delays in completion of military training more so than any other training-related injury. Furthermore, stress fracture recurrence poses a particular problem for military recruits, as it has previous been found that 10.6% of recruits with a history of stress fracture sustained a new stress fracture within one year of the initial injury. Disparities in stress fracture incidence are also known to exist based on both sex and race/ethnicity, but the origins of these discrepancies are poorly identified.

Our first aim (*Study 1*) is a cross-sectional study designed to determine differences in bone structure, bone quality, skeletal alignment and gait mechanics in female athletes with recurrent stress fractures (n=25), a history of one stress fracture (n=25), or no stress fracture history (n=25). The discrepancies in these parameters between groups will help to explain underlying differences in women who experience stress fracture recurrence.

Our second aim (*Study 2*) is a cross-sectional study designed to assess the race/ethnicity- and sex-based differences in bone structure, bone quality, and skeletal alignment in Asian, Black, and Caucasian men and women (n=40 for each group; n=240 total). This will serve to identify factors that contribute to the differences in stress fracture incidence due to race/ethnicity and sex.

Keywords: stress fracture, bone stress injury, gait analysis, bone microarchitecture, race/ethnic origin, sex-related differences, bone biomechanics, skeletal alignment

Accomplishments

Major Goals

The objectives, timeline, and status for the project are shown below in Table 1. Major goals for year 1 included obtaining approval from the Partners Institutional Review Board (IRB) and the Human Research Protections Office (HRPO), recruiting and enrolling participants in Study 1 and Study 2, acquiring and analyzing HR-pQCT images, performing standard whole bone finite element analysis, performing EOS and DXA scans and reference point indentation, performing biomechanical analysis, and beginning data cleaning and statistical analysis.

	Objective	Timeline	Site	Status
Study 1	1) Obtain Institutional Review Board (IRB) approval	Quarter 2	MGH	*Complete*
	2) Obtain Human Research Protections Office (HRPO) approval	Quarter 2	MGH	*Complete*
	3) Recruit and enroll 45 subjects [15 women athletes with multiple stress fractures, 15 women athletes with one stress fracture, 15 women athlete healthy controls; 15 in year 1-3]	Quarters 2-12	MGH	*Ongoing*
	4) Acquire and analyze high-resolution peripheral quantitative computed tomography (HR-pQCT) images for 45 subjects	Quarters 2-12	MGH	*Pending*
	5) Perform standard whole bone finite element analysis	Quarters 3-14	MGH	*Pending*
	6) Perform EOS and DXA scans and reference point indentation (RPI) for 45 subjects	Quarters 2-12	MGH	*Pending*
	7) Perform biomechanical analysis for 45 subjects	Quarters 2-12	SNRC	*Ongoing*
	8) Perform data cleaning and statistical analyses	Quarters 3-14	MGH, SNRC	*Pending*
	9) Renew IRB approval	Quarters 4, 8, 12	MGH, SNRC	*Pending*
Study 2	1) Obtain Institutional Review Board (IRB) approval	Quarter 2	MGH	*Complete*
	2) Obtain Human Research Protections Office (HRPO) approval	Quarter 2	USARIEM	*Complete*
	3) Recruit and enroll 180 subjects [30 per group: Asian women, Black women, Caucasian women, Asian men, Black men, Caucasian men; equal enrollment years 2, 3, and 4]	Quarters 2-12	MGH	*Pending*
	4) Acquire and analyze high-resolution peripheral quantitative computed tomography (HR-pQCT) images for 180 subjects	Quarters 4-12	MGH	*Pending*
	5) Perform standard whole bone finite element analysis	Quarters 5-14	MGH	*Pending*
	6) Perform EOS and DXA scans and reference point indentation (RPI) for 180 subjects	Quarters 4-12	MGH	*Pending*
	7) Perform data cleaning and statistical analysis	Quarters 5-14	MGH	*Pending*
	8) Develop race-, sex-, and age-specific databases of bone microarchitecture, reference point indentation, skeletal alignment, and gait mechanics	Quarters 5-14	MGH	*Pending*
	9) Renew IRB approval	Quarters 4, 8, 12	MGH	*Pending*

Table 1. Status of objectives and goals as listed in Statement of Work (SOW)

Accomplishments

Approval from the Institutional Review Board (IRB) at Massachusetts General Hospital (MGH) was received on February 24, 2017 and approval from Human Research Protections Office (HRPO) was received on March 10, 2017, respectively (Study 1, Objectives 1 and 2; Study 2, Objectives 1 and 2). These items were completed according to schedule. We will renew our IRB protocol in February 2018, and again in February 2019.

We recruited subjects for Study 1 via letters sent to patients with a stress fracture diagnosis as identified by their physician or the Partners Research Patient Data Registry, advertisements on the Partners Clinical Trials website, recruitment flyers posted in the greater Boston area, and recruitment emails sent to local running clubs and college coaches. Through these avenues, we enrolled a total of 21 female athletes for Study 1: two with multiple stress fractures, thirteen with a single stress fracture, and six without a history of stress fracture. All of subjects who were enrolled in the study successfully completed a study visit at the Spaulding National Running Center (SNRC), which included an analysis of their gait mechanics. We currently have 9 subjects scheduled to be enrolled in October 2017. An additional 22 subjects without a history of stress fracture are eligible according to their phone screen, and are ready to be enrolled. Recruitment outcomes and enrollment for Study 1 are shown in Figure 1 below. Analysis of the gait study for subjects who completed their SNRC visit has been ongoing during this reporting period, and is expected to continue through Quarter 12.

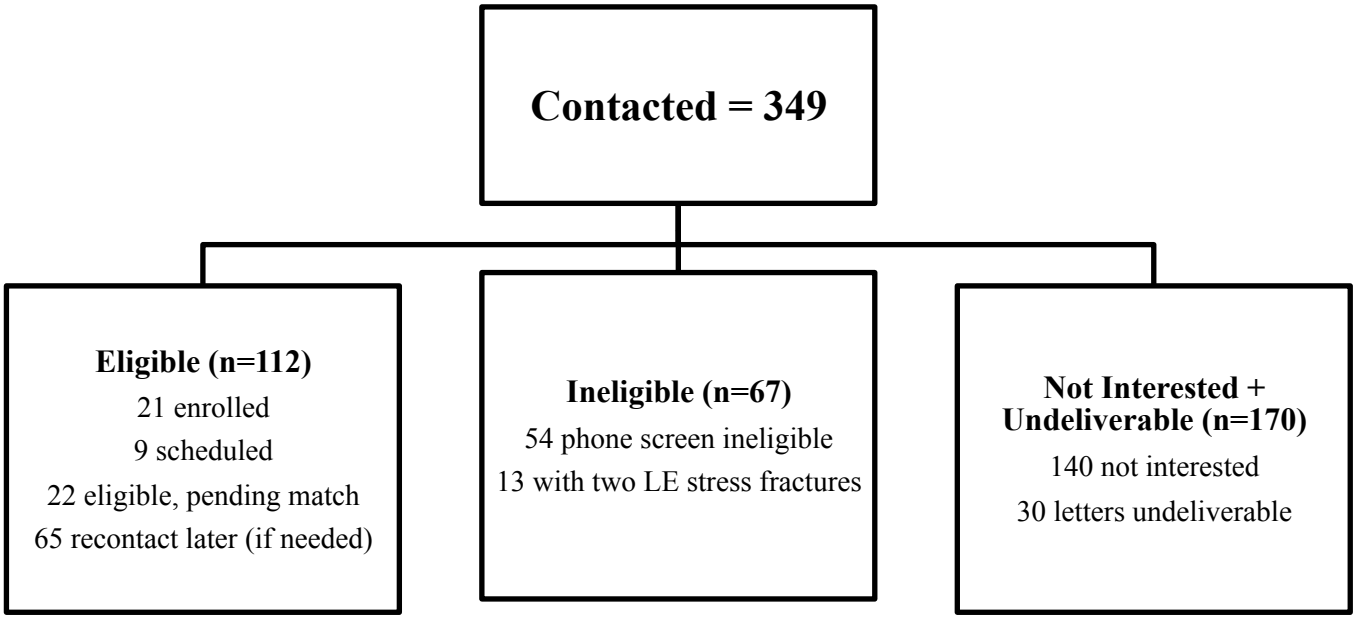

Figure 1. Recruiting efforts and enrollment for Study 1.

Other activities during this period included site preparation with the Translational and Clinical Research Center at MGH, where nurse practitioners will be performing the reference point indentation (RPI) procedure. Weekly study staff meetings, facilitated by the principal investigator, were also conducted during this period. Data entry and cleaning has also begun for Study 1, and is ongoing.

Opportunities for Training and Professional Development
Nothing to report

Dissemination of Results
Nothing to report

Goals for Year 2
We will continue recruiting and enrolling subjects in Study 1, and we anticipate that most will complete both study visits (one at SNRC, one at MGH) by Fall 2018 (Study 1, Objective 3). At the MGH study visits, we will assess bone microarchitecture by HR-pQCT imaging, perform whole body X-ray imaging to assess skeletal alignment, measure bone mineral density by DXA, and complete reference point indentation (Study 1, Objectives 4 and 6). Given that study visits are ongoing, we will begin analyzing HR-pQCT images and completing standard whole bone finite element analysis as these scans are acquired (Study 1, Object 5). Further, we anticipate that biomechanical analysis of the subjects enrolled in Study 1 will be complete by Fall 2018 (Study 1, Objective 8). Data cleaning is ongoing, and we predict that we will begin statistical analyses before the end of Year 2 (Study 1, Objective 8). We will also be renewing Partners IRB approval of the study protocol in February 2018 (Studies 1 and 2, Objective 9).

For Study 2, we will begin recruiting and enrolling subjects in Quarter 5 (Study 2, Objective 3). We do not anticipate any issues in achieving our enrollment target given the positive response we've seen for Study 1. We will begin performing HR-pQCT, DXA, and EOS scans, and reference point indentation, for Study 2 participants in the next reporting period (Study 2, Objectives 4 and 6), and will complete standard whole bone finite element analysis as these scans are acquired (Study 2, Objective 5). Data cleaning and statistical analysis for Study 2 is expected to begin by the end of Year 2 (Study 2, Objective 7). Development of race-, sex-, and age-specific databases of bone microarchitecture, reference point indentation, skeletal alignment, and gait mechanics (Study 2, Objective 8) will be initiated once statistical analysis for this study is underway.

Impact

Nothing to report.

Changes/Problems

There have been no changes to the approach of the study, expenditures, or in the use or care of human subjects. We have encountered a delay in beginning recruitment for Study 2 and in completing Study 1 visits at MGH, as we are still waiting for approval of placement of the 2nd generation HR-pQCT. However, we do not anticipate being unable to meet our overall target enrollment for Studies 1 and 2, and will be increasing our recruitment efforts in the next reporting period, as soon as the HR-pQCT device is installed, accordingly.

To resolve this delay, we are working closely with MGH facilities personnel and research space administration to secure a location for the 2nd generation HR-pQCT device.

Products

Nothing to report.

Participants and Other Collaborating Organizations

Personnel

Name:	Mary Bouxsein, PhD
Project Role:	Principal Investigator
Research Identifier:	N/A
Nearest Person-Month Worked:	0.72
Contribution to Project:	Dr. Bouxsein performed work in the areas of data and safety monitoring, study sponsor correspondence, study data and procedure review, and budget review.

Name:	Irene Davis, PhD
Project Role:	Site-Responsible Investigator
Research Identifier:	N/A
Nearest Person-Month Worked:	0.96
Contribution to Project:	Dr. Davis performed work in the areas of data and safety monitoring as well as study data and procedures review.

Name:	Kathryn Ackerman, MD
Project Role:	Co-Investigator
Research Identifier:	N/A
Nearest Person-Month Worked:	0.84
Contribution to Project:	Dr. Ackerman helped to identify potential subjects and assisted with data and safety monitoring, and data and procedures review.

Name:	Kristy Popp, PhD
Project Role:	Co-Investigator
Research Identifier:	N/A
Nearest Person-Month Worked:	2.28
Contribution to Project:	Dr. Popp performed work in identifying, recruiting, and screening potential subjects, obtaining informed consent, data and safety monitoring, study sponsor correspondence, study data and procedures review, and study budget review.

Name:	Matt Ruder, PhD
Project Role:	Research Technician
Research Identifier:	N/A
Nearest Person-Month Worked:	6.00
Contribution to Project:	Dr. Ruder performed biomechanical analyses for Study 1 subjects, as well as work in the areas of data and safety monitoring and review of data and procedures.

Name:	Signe Caksa
Project Role:	Research Coordinator
Research Identifier:	N/A
Nearest Person-Month Worked:	9.00
Contribution to Project:	Ms. Caksa performed work in identifying, recruiting, and screening potential subjects, obtaining informed consent, data entry, data and safety monitoring, maintenance of IRB documents, and review of study data and procedures for Study 1.
Funding Support:	DOD award number W81XWH-15-C-0024

Name:	Sara Rudolph
Project Role:	Research Coordinator
Research Identifier:	N/A
Nearest Person-Month Worked:	3.00
Contribution to Project:	Ms. Rudolph performed work in identifying, recruiting, and screening potential subjects, obtaining informed consent, data entry, data and safety monitoring, maintenance of IRB documents, and review of study data and procedures for Study 1.

Name:	Emily Orwig
Project Role:	Summer Intern
Research Identifier:	N/A
Nearest Person-Month Worked:	0.60
Contribution to Project:	Ms. Orwig performed work in identifying, recruiting, and screening potential subjects, obtaining informed consent, data entry, data and safety monitoring, and review of study data and procedures for Study 1.

Name:	Matthew Scott
Project Role:	Summer Intern
Research Identifier:	N/A
Nearest Person-Month Worked:	0.60
Contribution to Project:	Mr. Scott performed work in identifying, recruiting, and screening potential subjects, obtaining informed consent, data entry, data and safety monitoring, and review of study data and procedures for Study 1.

There is nothing to report regarding changes in active PIs or key personnel.

Partner Organizations

- **Organization Name:** Spaulding National Running Center
- **Location of Organization:** Cambridge, MA
- **Partner's contribution to the project:** facilities and collaboration; data collection for gait mechanics was performed at the Spaulding National Running Center. SNRC staff assist with study visits, data collection, and biomechanical data analysis.